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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/777,792
Filing Date: February 11, 2004
Appellant(s): SCHENK, DALE B.

Joe Liebeschuetz
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 18 August 2009 appealing from the Office action mailed 18 November 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

In the Appeal Brief, appellant identified three cases disclosing similar subject matter. Application 09/723765 has since issued as U.S. Patent 7,588,766, and has claims drawn to methods of treating Alzheimer's disease, whereas the present claims under appeal are drawn to compositions whose intended uses include such treatment. Neither 09/332289 nor 09/724319 is currently under appeal, and neither claims products which are Aβ fragments linked to toxoids, as in the present claims.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,262,332	Selkoe	11-1993
5,773,007	Penney	6-1998
5,733,548	Restifo	3-1998
5,723,130	Hancock	3-1998
5,601,827	Collier	2-1997

Wong, C.W. "Neuritic plaques and cerebrovascular amyloid in Alzheimer disease are antigenically related" Proc Natl Acad Sci USA vol 82, (1985), pp. 8729-8732.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

Claims 119, 121 – 125, and 131 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Selkoe (U.S. Patent 5,262,332), Wong 1985 (Proc. Natl. Acad. Sci. USA 82:8729-8732) and Penney (U.S. Patent 5,773,007).

Selkoe teaches methods of making antibodies to Aβ protein that are to be used for detection and diagnosis of disease. Specifically, at column 2 lines 36 – 44 Selkoe teaches methods of diagnosing Alzheimer's disease by contacting samples from patients with antibodies that are capable of identifying β-AP (beta amyloid protein) or "a β-AP fragment of about 8 or more amino acids". At column 3 line 51 – column 4 line 24 Selkoe teaches that fragments of "about 8 or more amino acid residues" can be used to make antibodies to β-AP. Thus the reference is on point to products for making antibodies that bind to Aβ consisting of fragments of "about 8" amino acids of β-AP. As residues 1 – 7 of Aβ, recited in claim 119, is a fragment 7 residues long, and 7 is clearly "about 8" residues, the reference is on point to independent claims 119 and 131. Selkoe teaches that up to 250 μg of protein can be administered for production of antibodies (column 17 lines 34 – 40), which is on point to claims 121 – 124. However Selkoe does not teach linking the fragment of the Aβ protein to a toxoid from a pathogenic bacterium as recited in claims 119 and 131.

Wong teaches conjugates for production of antibodies against Aβ. Specifically, Wong teaches a conjugate (called OP1) comprising residues 1 – 10 of Aβ conjugated to keyhole limpet hemocyanin (KLH, p. 8729 second column third complete paragraph – p. 8730 first

column), which is an antigen that can increase the immune system's reaction to the molecule to which it is conjugated. Wong teaches that the antibodies raised against this conjugate are useful for detection of Aβ and diagnosis of Alzheimer's disease. However Wong does not teach residues 1 – 7 of Aβ linked to a carrier which is a toxoid from a pathogenic bacterium as recited in claims 119 and 131.

Penney teaches that purified antigens are often not effective in eliciting an antibody response, and so to boost the response one should include an immunostimulant, such as the toxoid CRM 197, encompassed by claims 119, 125, and 131 (see column 1 line 63 – column 2 line 8). Penney teaches that any carrier molecule can be used, including Keyhole Limpet Hemocyanin (KLH) and any of several toxoids from pathogenic bacteria, including but not limited to CRM 197, which is a diphtheria toxoid (see column 5 first paragraph). Penney teaches covalent linkage, as encompassed by claim 125; see column 1 lines 8-12 and column 5 first paragraph, for example. Penney teaches that adjuvants can optionally be added to antibody-inducing compositions in order to mitigate any local hypersensitivity to the carrier (column 2 lines 7 – 15), which is on point to claim 131, part (b). However Penney does not teach conjugates comprising residues 1 – 7 of Aβ as encompassed by claims 119 and 131.

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to make a composition comprising residues 1 – 7 of Aβ peptide covalently linked to CRM 197, with a reasonable expectation of success. The motivation to do so would be to stimulate the host animal's immune system to make more antibodies, which could then be used in the diagnostic assays of either Selkoe or Wong. Selkoe teaches that "about 8" amino acids should be used in raising antibodies, and Wong points to the N-terminus of the Aβ protein as that region which is suitable for making antibodies to be used in diagnostic assays. Wong teaches that residues 1 – 10 of Aβ are to be coupled to a heterologous protein for the purpose of increasing antigenicity, so it would have been obvious to one of ordinary skill in the art to couple the shorter peptide (i.e., residues 1 – 7 of Aβ peptide) to a heterologous protein to increase antigenicity. Combining these teachings would have been obvious to one of ordinary skill in the art as both Selkoe and Wong teach making antibodies with these short peptides. Furthermore Penney teaches that CRM 197 can be substituted for KLH as a heterologous peptide used to increase antigenicity. Thus it would be reasonable to expect success.

Claims 119 – 125 and 131 - 132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Selkoe, Wong, and Penney as applied to claims 119, 121 – 125, and 131 above, and further in view of Restifo (U.S. Patent 5,733,548, of record).

The reasons why claims 119, 121 – 125, and 131 are obvious over Selkoe, Wong, and Penney are set forth above. However none of the references explicitly teaches a plurality of additional copies of the relevant antigen, as recited in claims 120 and 132.

Restifo discloses that multiple copies of a peptide can be included in order to increase the immunogenicity of said peptide, and that this method should be effective even in those cases where a single copy of the peptide itself is not antigenic (see column 4 lines 32-36 and column 5 lines 15-22). Thus the reference is on point to claims 120 and 132. However Restifo does not teach comprising residues 1 – 7 of Aβ as encompassed by claims 119 and 131.

It would have been obvious to one of ordinary skill in the art to include multiple copies of the antigen, as suggested by Restifo, with a reasonable expectation of success. The motivation to do so would be to increase the immune response to the peptide antigen. The artisan of ordinary skill would realize that a small peptide (i.e. one "about 8" amino acids long as taught by Selkoe) would be unlikely to elicit a strong immune response on its own. Additionally, the fact that Wong used immune-boosting KLH in raising antibodies to a slightly larger peptide (residues 1 - 10 of Aβ) indicates to the artisan of ordinary skill the need to increase the immune response to the peptide. Thus the artisan would have been motivated to include multiple copies of the antigen and would have found such an invention obvious.

Claims 119, 121 – 125, 131, and 133 – 138 are rejected under 35 U.S.C. 103(a) as being unpatentable over Selkoe, Wong, and Penney as applied to claims 119, 121 – 125, and 131 above, and further in view of Hancock (U.S. Patent 5,723,130, issued 3 March 1998).

The reasons why claims 119, 121 – 125, and 131 are obvious over Selkoe, Wong, and Penney are set forth above. Note that Selkoe teaches the doses recited in claims 134 – 137 and chemical cross-linking as recited in claim 138. Penney teaches that adjuvants, recited in claim 131, can be added to the compositions in order to mitigate hypersensitivity or to increase immunogenicity (column 2 lines 10-12 for example). However none of Selkoe, Wong, or Penney teaches the specific adjuvant QS-21 as recited in claim 133.

Hancock teaches QS-21 (recited in claim 133) is particularly suitable as an adjuvant as it increases the immune response, resulting in more antibodies that tightly bind to the antigen

administered (see column 2 lines 25 – 35 for example). However Hancock does not teach comprising residues 1 – 7 of Aβ as encompassed by claims 119 and 131.

It would have been obvious to one of ordinary skill in the art to select QS-21 taught by Hancock as the adjuvant to be included in the compositions rendered obvious by Selkoe in view of Wong and Penney, with a reasonable expectation of success. The motivation to do so would be to select an adjuvant known to be particularly effective in eliciting antibodies, which could then be used in the methods taught by Selkoe and by Wong.

Claims 119, 121 – 131, and 133 – 143 are rejected under 35 U.S.C. 103(a) as being unpatentable over Selkoe, Wong, Penney, and Hancock as applied to claims 119, 121 – 125, 131, and 133 – 138 above, and further in view of Collier (U.S. Patent 5,601,827).

The reasons why claims 119, 121 – 125, 131, and 133 – 138 would have been obvious to one of ordinary skill in the art are set forth above. However none of the references cited explicitly teaches fusion proteins *per se*, as recited in claims 128 and 141, or the specific N- and C-terminal linkages recited in claims 126 - 127, 129 - 130, 139 - 140, and 142 - 143.

Collier teaches vectors for production of diphtheria toxoids, such as CRM-197 (see column 1 final paragraph) and teaches that the vectors can be used for construction of fusion proteins between a diphtheria toxoid and an antigen (see column 4 final paragraph and column 9 final paragraph). The reference is thus on point to fusion proteins, as recited in claims 128 and 141, and is also on point to independent claims 119 and 131, which encompass diphtheria toxoid CRM 197. Collier teaches that construction of vectors for fusion proteins is well-known in the art, but does not explicitly teach the specific N- and C-terminal linkages recited in claims 126 - 127, 129 - 130, 139 - 140, and 142 - 143.

It would have been obvious to one of ordinary skill in the art to use the vectors from Collier to make fusion proteins between Aβ 1-7 and CRM 197, as rendered obvious by Selkoe in view of Wong, Penney, and Hancock. Collier teaches that the fusion protein method is particularly useful to produce those proteins which will be administered for production of antibodies, so it would be reasonable to expect success in using such methodology. Additionally, as Collier teaches that fusion proteins are generally known in the art, and re-arrangement of parts is generally not considered a patentable contribution (see MPEP § 2144.04(VI)), selection of either the N- or C-terminus of the Aβ fragment would have been obvious. Selection of a particular element from among a finite number of possible solutions

where the results are predictable can be considered obvious (see MPEP § 2143, section entitled "Exemplary Rationales" in discussing the Supreme Court's decision in *KSR International Co v. Teleflex Inc.*). Here, there are only 2 possible solutions (attachment at the N- or C-terminus), and Collier indicates that the fusion protein art was highly developed; note the patent to Collier was filed in 1995.

(10) Response to Argument

Appellant argues that the claimed products would not have been obvious to one of ordinary skill in the art, and the Examiner has failed to present a *prima facie* case of obviousness. Additionally, appellant argues that the claimed compositions have unexpected advantages, and therefore should be considered non-obvious even if a *prima facie* case had been made. Appellant makes the following points with respect to the examiner's rejection of independent claims 119 and 131, each of which will be addressed in turn:

A. No *prima facie* case of obviousness exists, and there was no motivation to either substitute CRM 197 or the fragment Aβ1-7 for KLH and the Aβ1-10 taught by Wong.

B. There are advantages to the presently-claimed products, which might not exist for the products in the prior art. These alleged advantages include superior results in human therapeutic administration (brief, pp. 12-13) and superior properties of antibodies raised against residues 1-7 of Aβ (brief, p. 11).

C. Selkoe suggests that antibodies should be raised against amyloid deposits, not small peptides.

D. The presently-claimed invention is distinguishable from certain cases relevant to determination of obviousness. (brief, pp. 13-14).

With respect to A above, the examiner respectfully disagrees with appellant that no prima facie case of obviousness exists. Selkoe clearly teaches one of ordinary skill in the art why antibodies should be made, namely for detection of Aβ and diagnosis of Alzheimer's disease; see abstract as well as column 2 lines 35-44. Selkoe also teaches one of ordinary skill that all or part of Aβ peptide (also called β-AP by Selkoe) can be used to immunize animals in making antibodies, and sets "about 8 or more amino acid residues" as the lower limit of Aβ peptide fragments to be used (column 2 lines 50-55). Wong teaches that the N-terminus of Aβ peptide, particularly the first ten amino acid residues, can be coupled to the immunostimulant

KLH and administered to animals in order to obtain antibodies. Penney provides the teachings that both KLH and CRM197 were known to be immunostimulants, which suggests that either of them could be used. Given that Selkoe sets "about 8" amino acids as the lower limit of Aβ peptide fragments to be used in generating antibodies, clearly contemplating some degree of breadth around 8, and given that Wong guides one of ordinary skill in the art to both select residues from the N-terminus of Aβ peptide and to couple to an immunostimulant, the invention as claimed would have been *prima facie* obvious to one of ordinary skill. Appellant argues that KLH is more suitable for administration to animals and that toxoids from pathogenic bacteria are more suitable for administration to humans (brief, p. 12). According to appellant, one of ordinary skill in the art would have had no reason to substitute one for the other, since none of the references cited teaches or suggests a therapeutic use for the composition in human patients. This argument is not persuasive; each of these elements (KLH and CRM 197, which is a toxoid from a pathogenic bacterium) was known to be effective for the same purpose, namely to stimulate the immune system. Although there may be slight differences between them, each was known to be an immunostimulant; see Penney column 5 first paragraph. Therefore substituting one for the other would have been obvious; see MPEP § 2144.06(II).

With respect to B, appellant argues that the claimed products are advantageous and therefore would not have been obvious to one of ordinary skill in the art. Specifically, appellant argues that "antibodies binding to an epitope within residues 1-7 of Aβ are particularly advantageous relative to antibodies with other epitope specificities" in assays relevant to treatment of Alzheimer's disease (brief, p. 11, first paragraph). Appellant is arguing about the advantages of different products from those claimed. Appellant is not claiming antibodies that bind within residues 1-7 of Aβ or methods of treating Alzheimer's or clearing plaques by administering such antibodies. Raising such antibodies for therapeutic purposes is one intended use of the claimed products, but intended uses are not given patentable weight. The compositions as claimed, which are obvious over the prior art of record, can also be used to make antibodies in animals, as taught by Selkoe and by Wong. Furthermore, the argument that the antibodies that bind to epitopes with residues 1-7 of Aβ have advantages over those that bind to epitopes in different parts of the molecule is not germane, since Wong's product, even if not modified following the guidance of Selkoe (who teaches that "about 8" amino acid residues should be present) would produce antibodies that bind to epitopes within residues 1-7 of Aβ.

Appellant also argues (brief, p. 12, final paragraph) that the claimed product "is an unexpectedly superior agent for human therapeutic administration than the Aβ1-10-KLH conjugate discussed by Wong." Again, appellant is arguing about an intended use of the product, not the product itself. The claimed product itself is an obvious variant of that disclosed by Wong. The claimed products differs from Wong's product only in that it lacks three amino acids (residues 8-10 of Aβ) and has a different immunostimulatory region (a toxoid from a pathogenic bacterium vs. KLH). The claimed product still would have been obvious to one of ordinary skill in the art, and would be expected to be effective in raising anti-Aβ antibodies, as disclosed by both Wong and Selkoe. Finally, the examiner notes that while appellant has asserted that the claimed conjugate has superior therapeutic effects as compared to that of Wong, no evidence of superior therapeutic effects have actually been presented.

With respect to C, appellant argues that Selkoe teaches that antibodies should be raised against amyloid plaques, not against small peptide fragments of Aβ. The examiner acknowledges that at column 21 lines 12-17 Selkoe teaches that antibodies raised against amyloid plaques are superior in detecting Aβ. However, immediately following this disclosure, beginning at line 18 Selkoe states that

> ... the latter synthetic fragment of the β-AP (comprising amino acids 1-28) or smaller β-AP fragments of 8 or more can be used as immunogens to produce peptide antibodies that can be used to detect skin β-AP deposits in AD [Alzheimer's disease] patients. Various discrete regions of β-AP... can serve as useful and specific antigens in the production of antibodies for immuno-detection of β-AP in skin.

Clearly, Selkoe does not teach away from using smaller fragments of Aβ. In fact, immediately after disclosing the superior nature of antibodies raised against amyloid plaques, he discusses how antibodies raised against the smaller fragments can be used. Reading Selkoe, particularly this section and the remaining sections where he teaches that "about 8 or more" amino acid residues can be used, one of ordinary skill in the art would have found the claimed antigenic constructs and compositions obvious.

With respect to D, appellant argues that the present case is distinguishable from *Pfizer, Inc. v. Apotex, Inc.* 82 USPQ2d 1321 and *Alza Corp v. Mylan Laboratories, Inc.* 80 USPQ 2d 1001. The examiner respectfully disagrees. In *Pfizer*, the issue was whether selection of a particular pharmaceutically acceptable salt, namely besylate, from among a list of 53 FDA-

approved anions would have been obvious or not. While the court recognized that some salts may not work, "the mere possibility that some salts may not form does not demand a conclusion that those that do are necessarily non-obvious." (*Pfizer* 82 USPQ2d at 1334) The court recognized that in some circumstances, selecting from among a finite number of known alternatives can be considered obvious. In the present case, since Penney explicitly lists both KLH and toxoids from pathogenic bacteria as immunogenic carriers to be coupled to antigens in order to increase antibody production (column 5 first paragraph), selecting one of these would have been obvious. Although clearly not all of Penney's disclosed carriers would be optimal, given the guidance provided by Penney, choosing a toxoid from a pathogenic bacterium would have been the result of routine experimentation. When a finite number of possible alternatives exists, selection from among those is reflective of obviousness, not a patentable contribution. In *KSR International Co. v. Teleflex, Inc.* 82 USPQ2d 1385, the Supreme Court stated that

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103. (*KSR*, 82 USPQ 2d at 1397)

The same logic applies to the present case. Since both KLH and toxoids from pathogenic bacteria were known to be effective in increasing immunogenicity, selecting either of these from among the short list of such immunstimulators disclosed by Penney would have been obvious. Similarly, *Alza* involved selection of auxiliary agents to go along with known products. The court ruled that selection of the particular auxiliary agent would have been obvious to one of ordinary skill in the art. Here, selection of one immunostimulatory agent or another would have been obvious, particularly given the teachings of Penney. Likewise, modifying the Aβ1-10 construct taught by Wong to be only the first 7, rather than the first 10 amino acids, would have been obvious given the guidance provided by Selkoe.

Appellant also argues that *Merck & Co. v. Biocraft Laboratories* (10 USPQ2d 1843) is distinguishable from the present case on its facts. According to appellant, "the claimed conjugates have an unexpectedly advantageous property relative to the art conjugates of

improved stability for human administration." (brief, p. 14, last complete sentence) Appellant provides no evidence of improved stability for this intended use. Appellant is claiming a series of products which could be used for human therapeutic administration, but could also be used for other purposes, including administration to animals in order to raise antibodies, as taught by Selkoe and by Wong. In *Merck*, the U.S. Court of Appeals for the Federal Circuit ruled that selection of one of many (1200) combinations disclosed in the prior art would have been obvious. Here, there are not nearly so many combinations to select from. Penney lists only a few immunostimulatory agents, including both KLH and the toxoids from pathogenic bacteria recited in the present claims, and teaches that they are each effective for the same purpose. If anything, the claimed invention involves considerably less picking and choosing than that at issue in the *Merck* case. One of ordinary skill in the art would have found the invention claimed as a whole, to be obvious in view of the cited prior art references.

Appellant did not separately argue the examiner's rejection of claims 119-125 and 131-132 as unpatentable over Selkoe, Wong, and Penney as applied to claims 119, 121-125, and 131 and further in view of Restifo (brief, p. 15, section 7.2). The rejection of claims 120 and 132 should stand or fall with the rejection of the independent claims set forth above.

Appellant argues, on pp. 15-16 of the brief, that the rejection of claims 119, 121-125, 131, and 133-138 as obvious over Selkoe, Wong, Penney, and Hancock should be overturned. According to appellant, the claims are non-obvious for at least the same reasons that the independent claims are non-obvious. Additionally, appellant argues that one of ordinary skill in the art would have had no reason to select QS-21, disclosed by Hancock to be an adjuvant in humans, for use in administration to animals as described by Wong. Wong used Freund's adjuvant, which is an adjuvant commonly used in animals but not used in humans. The examiner does not contest appellant's statements that Freund's is not routinely used in humans. Nevertheless, Hancock clearly teaches that QS-21 is an adjuvant (see for example column 2 second complete paragraph) and that its presence increases the amount of antibodies elicited by the immungen. In Hancock's case the immunogen was a protein from RSV. Of course the intended patient populations of Hancock and Wong are different. Hancock clearly is directed towards administering RSV vaccine to humans, whereas Wong teaches administering the immunogen to animals. But in each case, the adjuvants were added because they were known to increase the immune response and elicit more antibodies. See for example Hancock column 3 lines 3-7 and 19-22, as well as Wong p. 8730 first complete paragraph (note Wong teaches

that Freund's is an adjuvant, clearly meaning it increases immune response). Since each of these products (Freund's adjuvants, taught by Wong, and QS-21, taught by Hancock) was known to be effective for the same purpose, namely as adjuvants, substituting one for the other would have been the result of routine experimentation and improvement, not the result of a patentable contribution over the prior art. See MPEP § 2144.06(II).

Appellant did not separately argue the examiner's rejection of claims 119, 121-131, and 133-143 as unpatentable over Selkoe, Wong, and Hancock as applied to claims 119, 121-125, and 131, and 133-138 and further in view of Collier (brief, p. 17, section 7.4). The rejection of claims 126-130 and 139-143 should therefore be upheld for at least the same reasons. Note that Collier explicitly teaches fusion proteins between diphtheria toxins and antigens, as recited in claim 128 and 141. Even if the board were to determine that claims 133-138, drawn to QS-21 as the specific antigen, are non-obvious over Hancock, the present rejection of claims 128-130 should be maintained given the express teachings of Collier and appellant's failure to rebut.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Daniel E. Kolker/

Primary Examiner, Art Unit 1649

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/Jeffrey Stucker/

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